Bases embriogênicas da persistência dos sistemas retiniano e hialoide embrionários

Embryogenic foundations of the persistence of the embryonic retinal and hyaloid systems

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RESUMO

Os autores apresentam o relato de quatro casos de persistência completa do sistema retiniano e hialoide embrionários (PCSRHE), discutem sua patogenia baseados na embriogênese comparada procuram esclarecer os problemas que surgem no diagnóstico diferencial nos casos de leucocoria e sugerem o abandono da designação de *persistência do vítreo primário (VP) hiperplásico*. As razões para esta última proposta são as seguintes: 1) Não é só o VP que persiste, mas, também a retina embrionária, e a vasculatura hialoide com a haste do nervo óptico, ou restos desses elementos. 2) A palavra *hiperplasia* tem significado restrito em patologia, pois compreende somente os processos proliferativos não tumorais das células. Ora, tanto o vítreo primário como o secundário, definitivo do adulto, têm poucas células, as quais não aparecem como participantes da patogenia; além disso, o VP, nos casos de persistência completa, é escasso, portanto, hipoplásico, sendo um contrassenso a expressão *vítreo primário hiperplásico*.

UNITERMOS: Sistemas Retiniano e Hialoide Embriogênicos, Persistência, Diagnóstico Diferencial, Leucocoria.

ABSTRACT

The authors report 4 cases of Complete Persistence of the Embryonic Retinal and Hyaloid Systems (CPERHS), discuss their pathogeny based on compared embryogenesis, and attempt to clarify the issues that come forth in the differential diagnosis in cases of leukocoria, suggesting that the designation of Persistent Hyperplastic Primary Vitreous (PHPV) should be abandoned for the following reasons: 1) It's not only the Primary Vitreous (PV) which persists but also the embryonic retina as well as the hyaloid vasculature with the optic nerve stalk, or the remains of these structures. 2) The term hyperplasia has a restricted meaning in Pathology as it encompasses only nontumoral processes of cell proliferation. However, both the primary and the secondary vitreous have few cells, which do not appear as participants of the pathogeny; moreover, the PV in the cases of complete persistence is scarce and therefore hypoplastic, the designation Hyperplastic Primary Vitreous being nonsensical.

KEYWORDS: *Embryonic Retinal and Hyaloid Systems, Persistence, Differential Diagnosis, Leukocoria.*

INTRODUCTION

The present paper aims to clarify the problem of the differential diagnosis of retinoblastoma and Coats' disease in cases of leukocoria, with the persistence of the embryonic eye systems. Some cases of CPERHS lead to enucleation with the diagnosis of retinoblastoma. At present, complementary tests with more advanced procedures shall reduce the incidence of errors. Furthermore, it is important to get to know the mechanisms that cause the embryonic structures to persist after birth, when they should have undergone regression.

MATERIAL AND METHODS

The method used here consisted in comparing histological sections performed on rat embryos – from the Pathologic Anatomy Laboratory of the Medical School of UFRGS – and on leukocoric children's enucleated eyeballs, from the Eye Pathology Laboratory, a private institution.

Concerning the genetic involvement, we carried out a bibliographical review of the research done on this topic by several authors.

The opening of the eyeballs must not be performed haphazardly but according to the lesion that is expected. Both without fixation and after immersion of the piece in the fixatives currently used in Laboratories of Pathology, the vitreous, being too fluid, drains off or retracts and the eye ball gets deformed.

In order to avoid these inconveniences we used the following protocol.

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PROCEDURE TO PRESERVE THE VITREOUS IN SECTIONS OF THE EYEBALL

(Carlos Oswaldo Degrazia)

1. Fix the eyeball for two or three days;
2. Rinse it in tap water for at least 24 h. If the fixative contains picric acid, extend the rinsing until the yellowish color disappears in the water;
3. Place the piece in a container with alcohol at 60º C for 24 h;
4. Transfer it to alcohol at 70º for 24 h;
5. And finally to alcohol at 80º for 48 h.

The piece is then ready to be cut with a highly razor blade

HOW TO PROCEED TO THE CUTTING

A: 1. Firm the piece in a material with cork-like consistence. Headed pins can be used.

2. Make two parallel cuts in the anteroposterior direction, respecting the lens in either side. The result is two calottes and a central ring containing the lens in the anterior portion and the optic nerve in the posterior one. Up to 6 parts can be obtained, if need be.

B: Make a single cut, passing by the side of the lens. Two calottes are obtained, one of them with the lens.

C: Equatorial cut – Two parts are obtained. One encompass the posterior pole, with the macula and papilla, which can be easily examined. The other displays the relations between the posterior face of the lens, the ora serrata, and the ciliary processes. The anterior chamber and the cornea lie in the front.

D: In cases of lesions or tumors in the bulbar conjunctive or orbit, around the optic nerve, other cuts can be performed. In leukocorias, and most of the times, the anteroposterior direction is preferred, avoiding the risk of impairing the diagnosis of persistence of the hyaloid system, as the course of the optic nerve stalk will not be seen. In sending the piece to the laboratory, the surgeon must mark out with a black thread the insertion of the musculus rectus. The pathologist, aware of the clinical protocol, may rotate the eyeball and make the proper cut according to the case.

COMMENTS

A. Preliminary embryological approaches: developmental phases and their pathogenic implications

The *fundamental biogenic law* of Müller (1821-1897)/ Haeckel (1834-1919) (9), according to which ontogeny is a brief recapitulation of phylogeny – which means that we find similar embryonic forms in distinct species – expresses very accurately the existence of a common development plan for all living beings. French naturalist Louis Agassiz (1807-1873) (1), a creationist, called it *Divine Plan*.

We can say that: *For a general plan fitting all living beings to exist, it is necessary to use identical "tools" (drives) for giving rise to the large biotic diversity.* The search for animal models for understanding human structures dates back to ancient times, and the doubt-ridden question of whether *it is possible to apply to man what we see in the embryos of animals* can be answered in the affirmative in the light of the present knowledge. We should not look for equality in the comparisons, because from a given point on, the *specific* genetic systems impress the forms that characterize the different species. The morphological similarities found, however, are of such order that they allow comparison and generalization. The field is open to the application of protein antigens for the identification of the diverse groups and cell and tissular systems in the classification of living beings and their evolution.

Nineteenth-century scientists eagerly tried to find the vermiform stage of mammal and human embryos. Several contemporary universities or private institutions work with the embryonic development in animals and in humans. Some of these have websites with photo or drawing galleries depicting the embryos in several stages (a search can be made on the Internet using search words including the term *embryo*). In looking at these presentations we see no worm shapes. The many mammal species display, in their early weeks, embryonic forms resembling the *chordata* – the first step in the evolutionary scale of the chordates is represented by the *amphioxus* – and the vertebral column replaces the notochord in the higher vertebrates.

The word *development* – which designates the increase in the volume of a living being – applies to the embryo that evolves in shape and size, commanded by a strict genetic plan, the mechanism of which is complex. The genomic structure of many species, even of man, is entirely known. But its physiogeny is not. Benign and malignant tumors also increase in volume, but their growth surpass the tissular limits traced for the species. This is what we are taught by cell biology (*See* Bruce Alberts, Dennis Bray, Alexander Johnson (et. al.): Essential cell biology: an introduction to molecular biology of the cell. Garland Publishing, Inc., New York & London, 1998. Page 637 of the Portuguese translation. Editora ArtMed. Porto Alegre, 1999).

In every viviparous vertebrate, two clear-cut periods are manifest: an intrauterine period and a period that begins at birth and extends up to the adult state. Each period is liable to development deviations, with distinctive malformations.

The delimitation of what is considered as the embryo and the fetus is not clear. On page 15 of *Ocular Anatomy,*

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Embriology and Teratology (ed. by F. A. Jacobiec, Harper & Row Publishers, Inc.: 1982, U.S.A), Victoria Ozanics and Frederic A. Jacobiec reported data from the Columbia University that represent the mean of results obtained in several works. They considered as embryonic period in humans the one that goes from the first days to the 8th week (56 days), when the embryo reaches the size of 31-34 mm, corresponding to the length of 1 months and 26 days. Still, there are other ways of ordering the several stages of the intrauterine period. Smith C. G. et al. (16) present a classification in four stages, with the corresponding possible anomalies. At stage I, or first month, after *evagination* of the floor of the 3rd ventricle, there begins the formation of the optic cup, the lens, the vitreous and the vessels. At stage II, corresponding to the 2nd and 3rd months, the primary vitreous is already well-formed as well as the stalk of the optic nerve, which leaves the optical hole to cross the orbit centrally and penetrate the optic cup, reaching the posterior face of the lens (Figure 1c).

We call *Hyaloid System* in the embryo the primary vitreous, the stalk of the optic nerve with the hyaloid artery, the capillary ramifications of the vitreous periphery, and the *tunica vasculosa lentis*.

The term hyaloid means transparent as glass. In Greek, ὑαλὸς = glass. The primary and secondary or definitive vitreous, therefore, are hyaloid like the embryo's artery, which is the only one called hyaloid. The embryonic retina, which will form the double ciliary epithelium – one of the layers without pigment – the posterior face of the Iris and the monostratified pigmented epithelium of the adult retina, which is called, at this phase, Schwalb's epithelial retina, or *retinal neuroepithelium*. In the development of the embryo there are two opposing mechanisms to which we must pay attention: first, there is the evagination of the neural tube which gives rise to the primary optical vesicle. Soon afterwards there comes the invagination of the distal, lateral wall of this vesicle, resulting in the secondary optical vesicle, or simply, *optic cup*. There is a close correspondence between the layers lining the three formations: 1) The *marginal* layer of the neural tube, acellular and with a lamellar and fibrillar appearance, receives the optic nerve fibers originating from the ganglionic cells. 2) the cell-rich, medial layer is termed mantle – in French, *couche palleale* – corresponds to the *nervous retina*, and 3) the *germinative* layer lining the neural tube internally is homologous to Schwalb's epithelial retina, from which will arise the monostratified pigmentary epithelium of retina and iris, as well as the bistratified epithelium of the ciliary processes.

Upon invagination, the positions of the layers get inverted, and what was external in the primary vesicle becomes internal in the optic cup and vice-versa.

The hyaloid artery (HA) starts from a branch of the internal carotid and penetrates the optic stalk. Soon after passing the sclera it branches out in numerous capillaries which open and surround the primary vitreous (PV) in the anteroposterior direction, forming a vascular cup. At the end of the path it forms a vascular tuft, or bouquet, that encloses the lens – it is the *tunica vasculosa lentis* – until its anterior face, where it forms the *smaller vascular circle*, as the anterior face of the lens is not covered by vessels (Figure 1). These are capillaries with many anastomoses, which make connections with capillaries that form the *greater arterial circle*, which circumscribe the anterior part of the eye, at the bottom of the ciliary processes. There are multiple anastomoses between the HA capillaries and the ciliary arteries, communicating the two arterial circles.

The persistence of the hyaloid system occurs when the involutional phenomena of this system is interrupted, a period that is still poorly understood. For Victória Ozanics and Frederick Jacobiec (ibid., p. 80), HA regression takes place at the end of the 3rd month.

Figure 1 shows pictures of the hyaloid system of rat embryo. Due to the inclination of the piece, the cuts did not reach the pathway of the optic stalk, which, nonetheless, can be seen in Figure 1c; the *tunica vasculosa lentis*, however, appears almost complete. The missing anastomotic capillary net reappears in the next section.

The anatomical arrangement in animals may be slightly different from the human one, but the general plan is the same.

B. Complete Persistence of the Embryonic Retinal and Hyaloid System (CPERHS)

The reason why we use the phrase *Complete Persistence of the Embryonic Retinal and Hyaloid Systems* – substituting the one proposed by Reese (1955), (STEWART DUKE-HELDER, System of Ophthalmology, Vol. III, PART 2, p 771), used in the English literature, namely, *Persistence of the Hyperplastic Primary Vitreous* – is based on the following reasons: 1– it does not refer to the involvement of the embryonic retina, of the hyaloid artery with all the capillary branches including the *tunica vasculosa lentis*. 2– the correct meaning of hyperplasia is not in keeping with the referred lesion, as what is seen is the persistence of a very scanty PV, retained within the retracted embryonic retina (see Figs. 4e and 6d).

Considering Reese's authority and the extensive use of the phrase in the ophthalmologic practice, however, we believe the substitution will be difficult. In the same book, on page 765, it is mentioned that Meisssner (1855) would have described the lesion for the first time and Saemisch and Zehender made the ophthalmoscopic inspection in 1863, and since then the literature on the subject is immense. If the literature in 1964 – the date of publication of the cited treatise – was already extensive, as the book points out, imagine today, with the numerous existing scientific institutions! Other designations are also used, such as *Persistence of fetal vasculature*, etc. (5).

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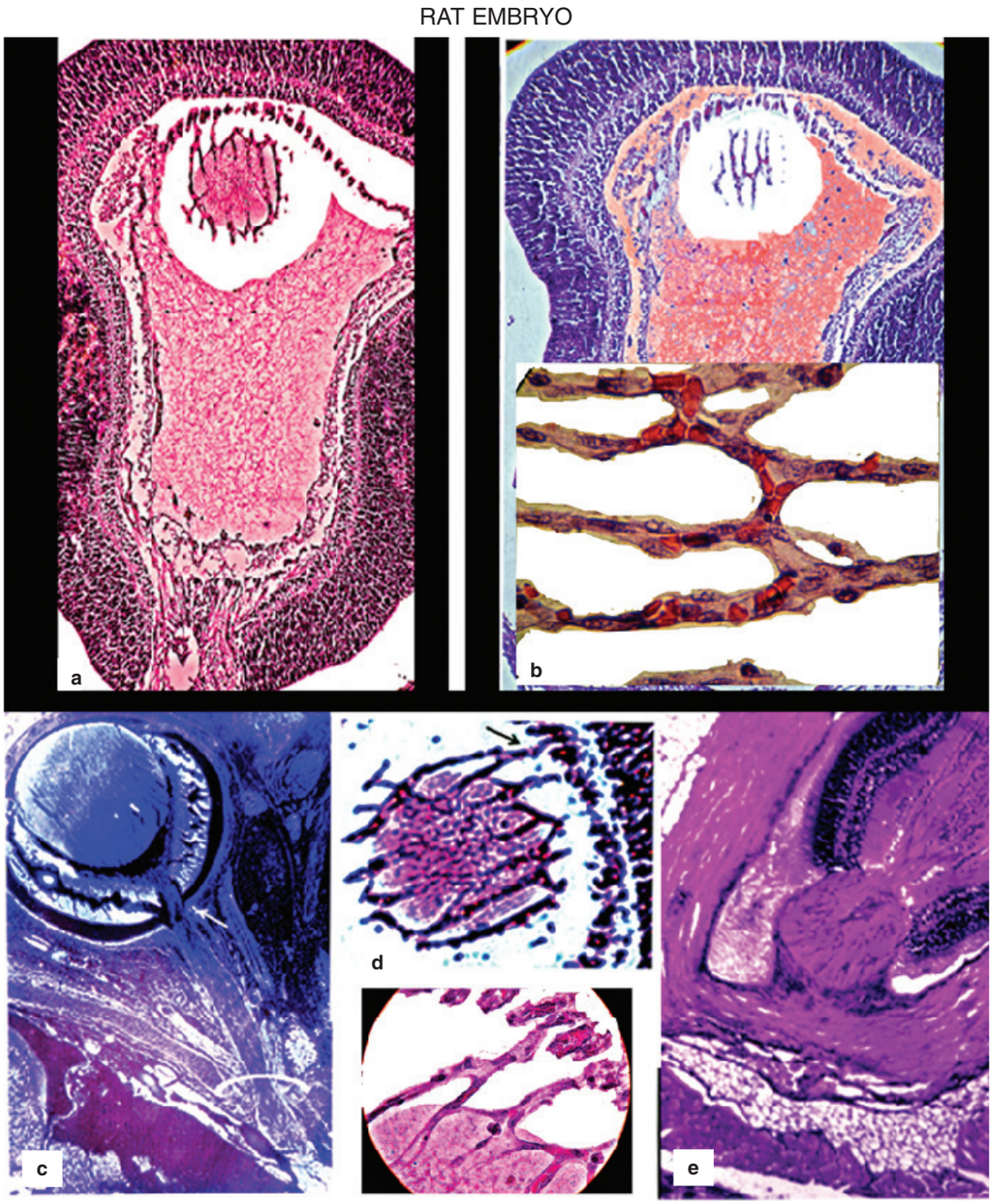


FIGURE 1 – a) The primary vitreous is kept within a sac formed by the hyaloid membrane. The sac is embedded in a vascular cup, arising from the hyaloid artery, which forms, at the entrance of the eyeball, a capillary tuft which expands. The mouth of the cup is partially covered by a concave capillary set, which in the sections takes the shape of a ring, the smaller vascular circle. The trajectory of the hyaloid artery is not seen due to the slant of the bloc. It forms, anteriorly, another capillary tuft that involves the lens constituting the tunica vasculosa lentis, which anastomoses into the capillaries forming the smaller (capillary) vascular circle and the larger vascular circle. The vitreous in the median portion is devoid of vessels, and usually takes an almost neuter coloration. The orange-red color of the picture was enhanced in the computer. Magnification: 20x. HE Stain. b) The serial section shows a group of capillaries which could be embedded into the missing portion of the tunica vasculosa lentis, in the picture beside. An intricate anastomotic net and the cells composing it can be seen. An adventitious membranaceous cell was highlighted. INSET: The same capillary net. Magnification 100x (plus photographic enlargement.) c) Section showing the trajectory of the embryonic optic stalk, which leaves the encephalic cavity, traverses the optical hole (semicircle), goes all the way through the orbit and pierces the cup (white arrow) up to the lens. d) Image enlargement for the purpose of showing the anastomoses (arrow) of the tunica vasculosa lentis with the capillaries comprising the greater capillary vascular circle. e) Transversal section of the embryonic optic stalk, inside the optic cup and beside the future papilla.

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CASE 1

Leukocoria of the right eye in a 3-year old boy. Clinical suspicion of retinoblastoma.

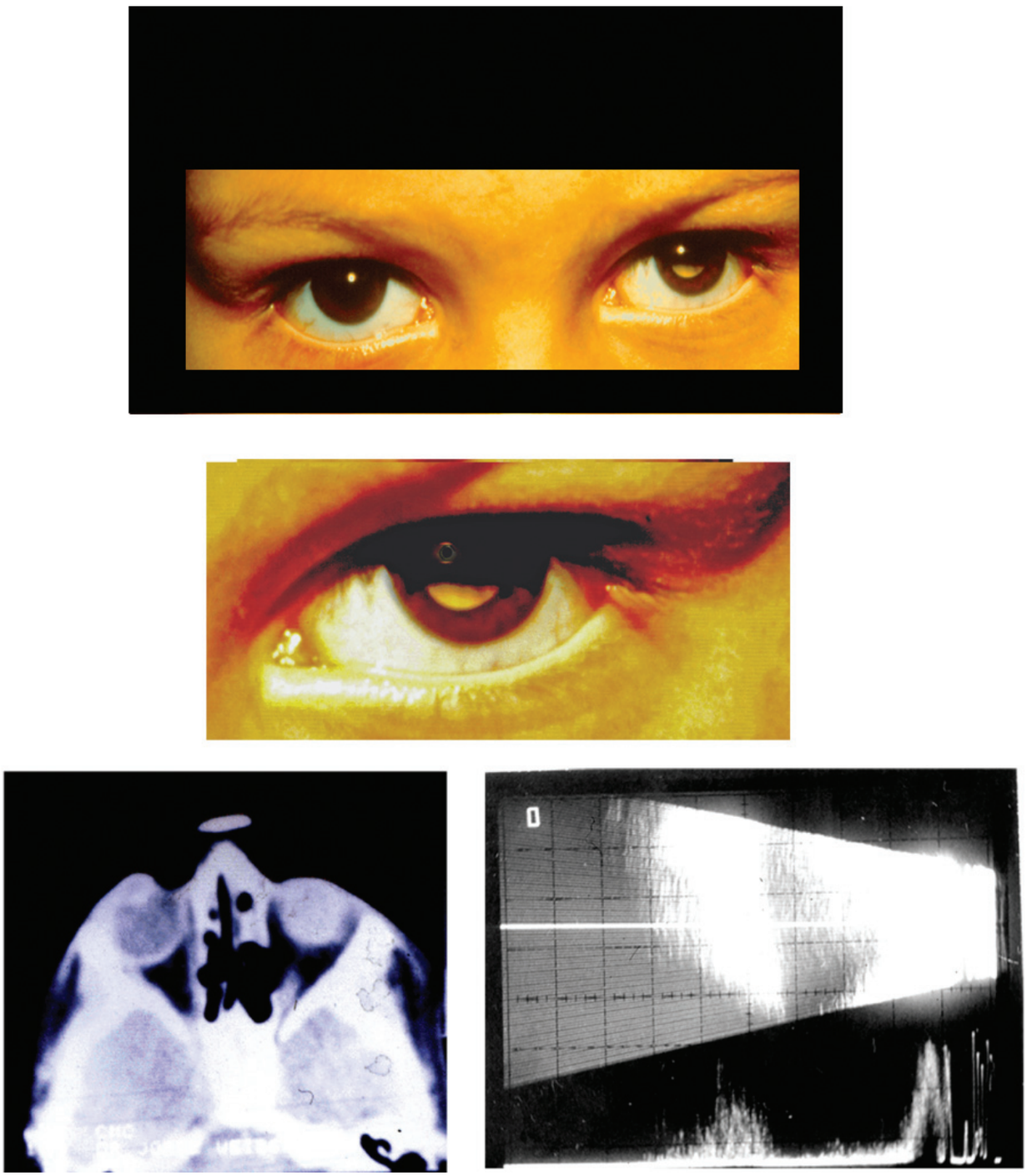


FIGURE 2

Complementary tests: CT scan: Opacification of the right eye with microphthalmia, which is not compatible with retinoblastoma. Non-elucidative ultrasonography.
Tests: Lab.: Eosinophilia. Lymphocytosis. Elevated alkaline phosphatase.

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CASE 1 (Macroscopy and Microscopy)

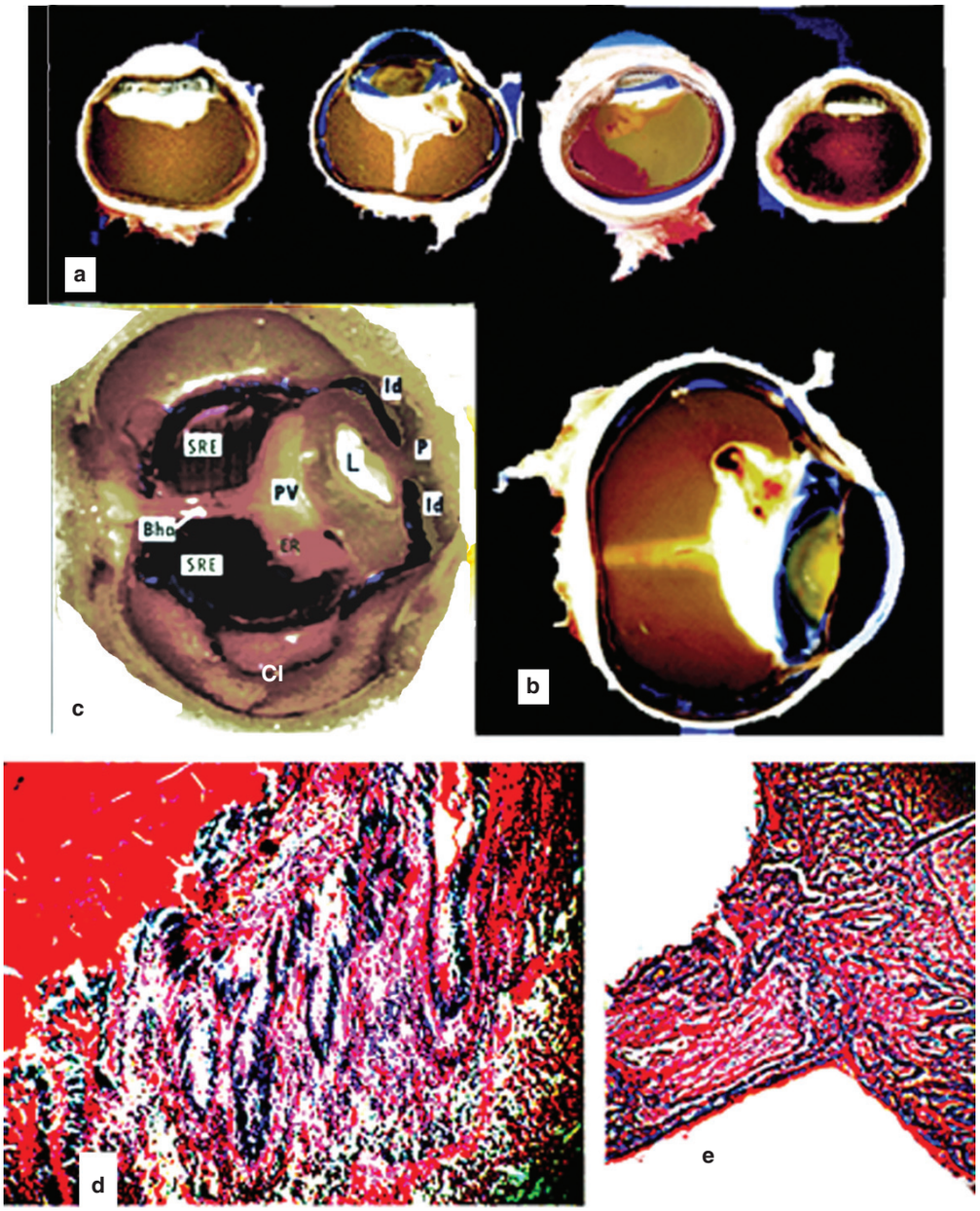


FIGURE 3 – **Macroscopy** (Like the stages of a tornado): a) The eyeball was divided in four pieces: two lateral calottes and two central rings, allowing an extensive internal inspection. In one of the rings one notes a funnel-shaped whitish mass that compresses the lens, and whose stalk, posteriorly, is continuous with the optic nerve. All the ball is filled with coagulated subretinal exudation, semitransparent and citrine yellow in color. Maybe confused with primary vitreous PV. There are haemorrhagic areas in one of the quadrants. b) Amplification of the median piece with the persistent optic stalk and part of the visible hyaloid artery. c) Photograph of the paraffin bloc with the purpose of showing the structures of the hamartoma: Bha: Bed of hyaloid artery in the embryonic optic stalk, sometimes confused with Cloquet's canal – SRE: Subretinal exudation – PV: Embryonic primary vitreous and retina – L: Lens – ID: Iris Diaphragm – P: Pupil – ER: Embryonic retina – Cl: Clot.

Microscopy: d) Histological section of retrolental whitish mass, showing the neuroepithelium with numerous folds giving it the aspect of dysplastic retina. e) Section involving the stalk and part of the retrolental mass. The mass is involved by the embryonic retina (neuroepithelium) – resembling retinal dysplasia.

Anatomopathologic diagnosis: Complete Persistence of the embryonic retinal and hyaloid systems.

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CASE 2

4-year-old boy with blind right eye, with yellowish, grayish white mass and surface vessels. The mother reports the classic amaurotic cat's eye brilliancy. Clinical suspicion of retinoblastoma.

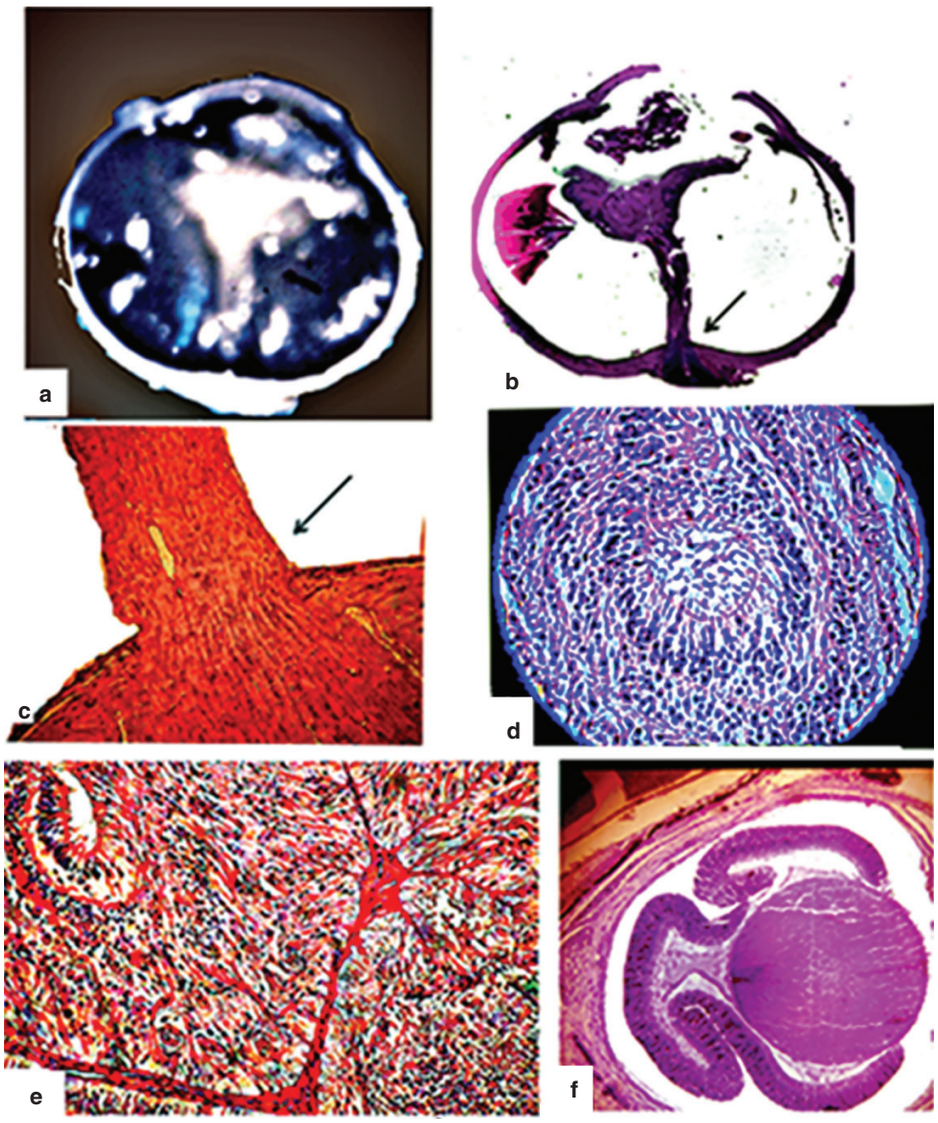


FIGURE 4

Macroscopy: Dimensions: anteroposterior 20 mm. Equatorial 17 mm. a) In the section, see the slightly yellowish, grayish white mass behind the lens. From it arises the thin stalk up to the area of the papilla, where it continues with the optic nerve. Irregular in shape, the mass involves the lens so as to make it invisible. b) A section of the bloc mounted on a slide showing the entire route of the persistent optic stalk.

Microscopy: c) Section at the base of the optic stalk penetrating the eyeball, in the region corresponding to the papilla. See a small portion of the hyaloid artery bed and the glial fibrils characteristic of the optic nerve. The arrows indicate the correspondence of the sections in b and c. d) A rosette closely resembling those of retinoblastoma, and which may subject to confusion. The limiting membrane can be seen quite clearly. In fact it is a cross section of the bottom of a fold, or crypt. HE, magnification 40X. e) The folding of the embryonic retina presents with the typical aspect of a drainage basin with tributaries and lakes. This structure is common to the four cases presented. In the left top corner there is a palisade of cells characteristic of the embryonic neuroepithelium. f) Embryonic eyeball of laboratory rat. This figure serves to compare the embryonic development, showing the embryonic retina and its neuroepithelial structure, as well as the histological aspect of the retrolental mass of the patient. Because of the technical handling, the retraction separated the anterior retina from the ciliary processes. Similarly, the gap formed by the invagination of the inferior part underwent a small solution of continuity. Coupled to the entire wall of the eyeball is the pigmentary epithelium of the retina, which is not seen in the preparation.

Anatomopathologic diagnosis: Complete Persistence of the Embryomic Retinal and Hyaloid Systems (CPERHS).

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CASE 3

7-year-old white boy presented with leukocoria in the right eye. Routine tests showed mass in the posterior chamber with neovascularization.

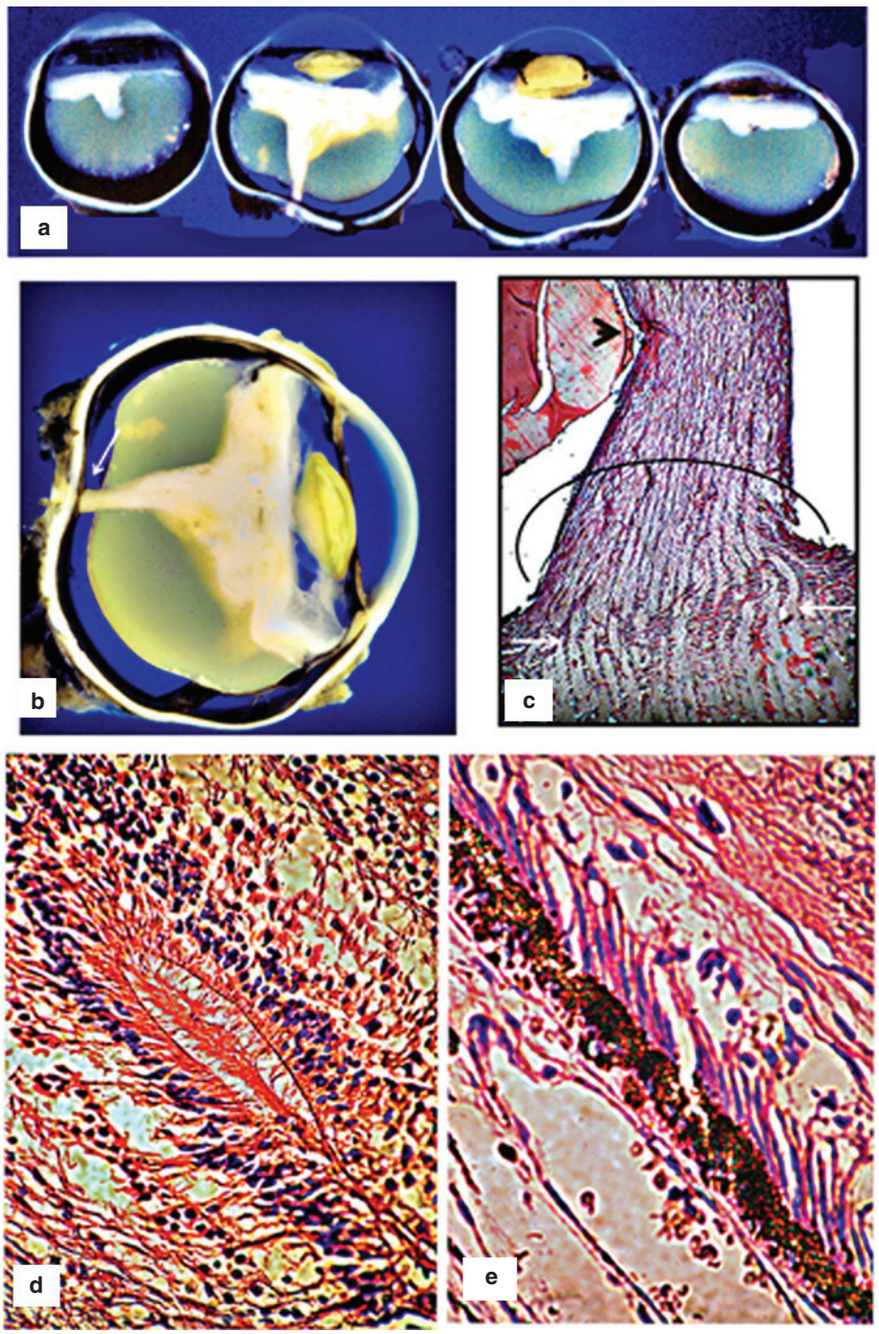


FIGURE 5

Macroscopy (Like the stages of a tornado): Dimensions: anteroposterior 20 mm. Equatorial 22 mm. a) The eye ball was sectioned in four parts: two central rings and two calottes. See the detached retina in tornado-shape behind the lens, with the vortex in the papillary region. The subretinal fluid is greenish. Maybe confused with primary vitreous. b) The magnified image shows the entry of the persistent hyaloid system (arrow) into the eyeball.

Microscopy: c) Section showing the persistent optic stalk (semicircle), crossing the sclera in the lamina cribrosa (white arrows). The arrowhead shows a slight inflexion of the stalk, pushed by the subretinal exudation. d) Palisade of cells of embryonic retina, with limiting membrane. e) Pigmentary epithelium showing structures similar to anomalous cones and rods.

Anatomopathologic diagnosis: Complete Persistence of the Embryomic Retinal and Hyaloid Systems (CPERHS).

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CASE 4
ADULT WITH COMPLETE PERSISTENCE (CPERHS)

46-year-old white female. At age 21 suffered trauma in left eye followed by painful glaucomatous crises.

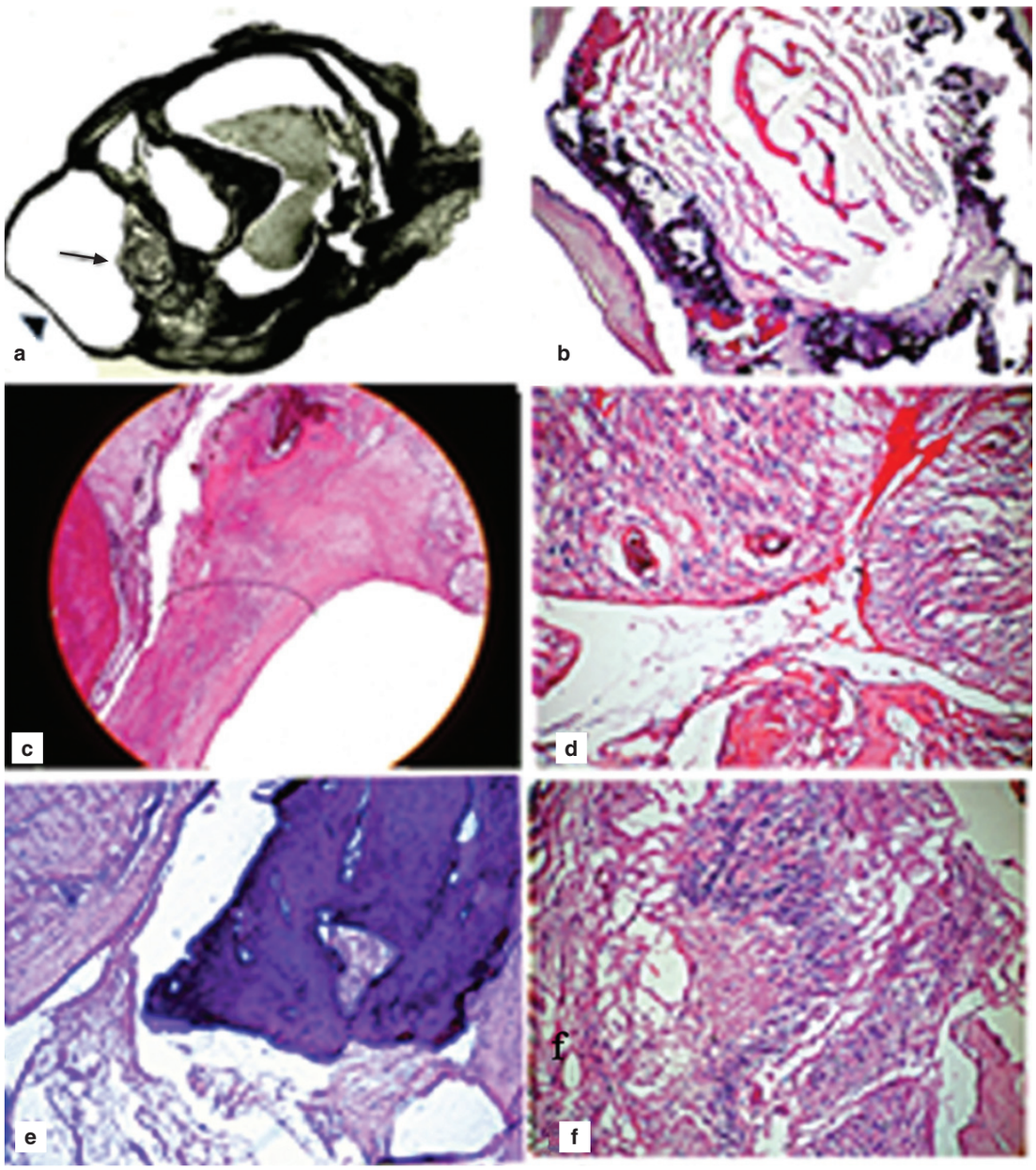


FIGURE 6

Macroscopy: Dimensions: anteroposterior: 28 mm. Equatorial: 26 mm. (Buphthalmia). Section surface shows empty anterior chamber. Lens opaque and retracted. Posterior chamber full of opalescent coagulated fluid.

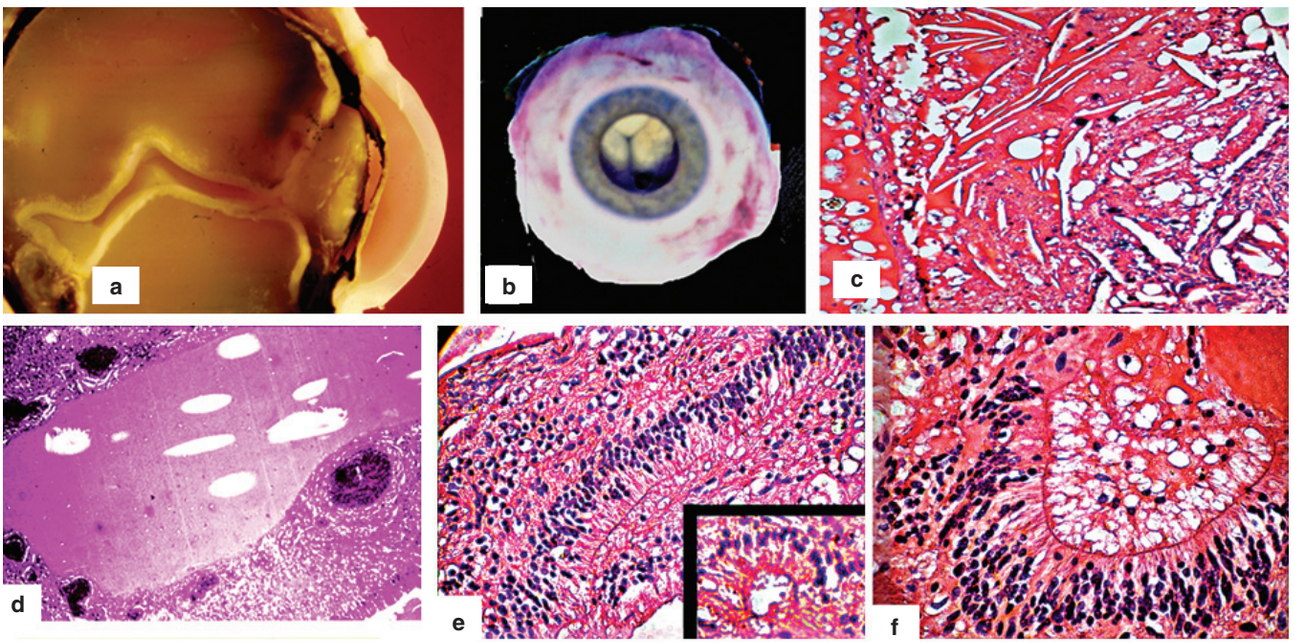
Microscopy: a) Section of the specimen mounted on wide slide. Anterior chamber is an ample cavity, anteriorly limited by the thinned cornea (arrowhead). The arrow inside the chamber indicates the lens. b) Lens observed at a magnification of 20 x and HE staining. Note the calcium deposits throughout the cortical. The nucleus presents extensive hyaline degeneration. c) The semicircle indicates the persistent optic stalk, pushing against the sclera, and ending in the retrolental mass. d) Typical drainage basin similar to the one described in Fig. 4 e. e) Extensive ossification of the posterior pole. f) Mass of detached embryonic retina infiltrated by elements compatible with glial cells and glial fibrils.

Diagnosis: The microscopic aspects in c and d are pathognomonic for CPERHS.

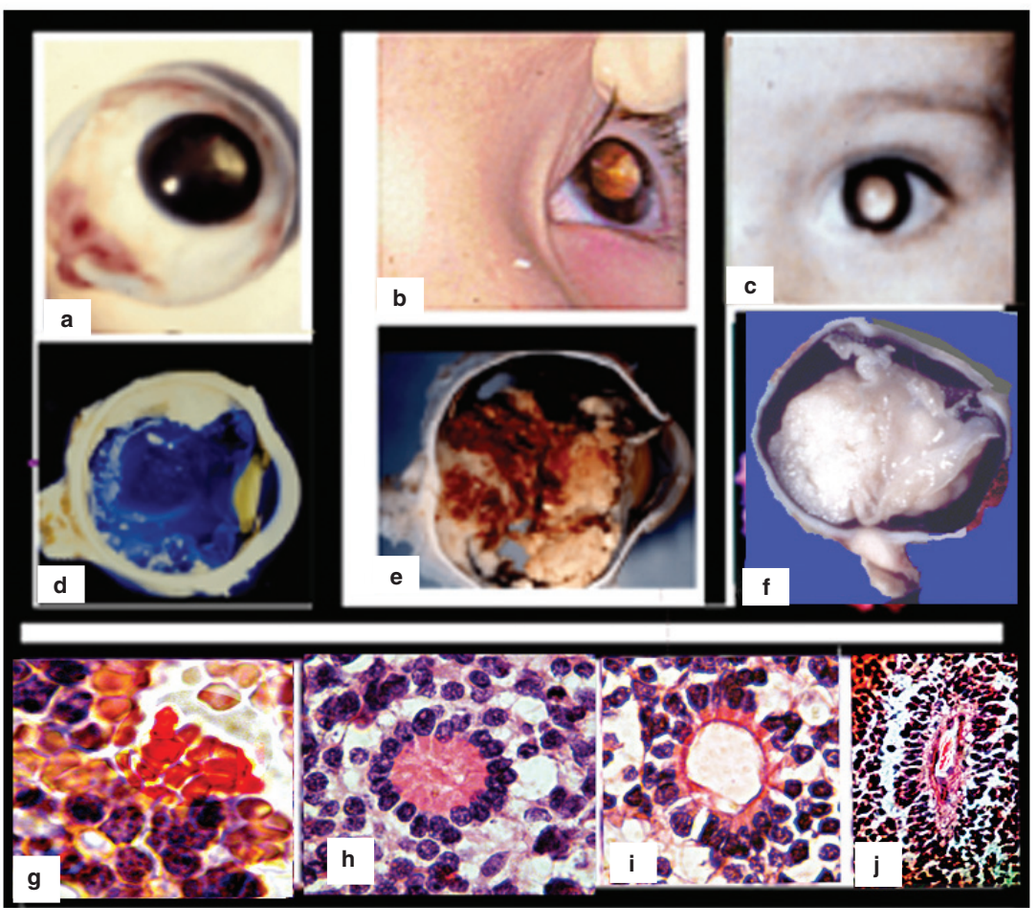
Note: It is a rare case being an adult with intraocular hamartoma.

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DIFFERENTIAL DIAGNOSIS
Coats' disease



RETINOBLASTOMA



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CHARACTERIZATION IN THE GENERAL PATHOLOGY

The CPERHS is a hamartoma (Greek αμαρτανηεν, amartainei or "Hamartia" = to make mistakes) – a term introduced by F. Albreich (1904) (2) to designate tumoral or pseudo-tumoral malformation that is produced solely at the expense of local tissues. A choristoma is a malformation with tissues that are extraneous to that site.

PRESENTATION

The great majority of cases present as a sporadic unilateral congenital form, referred to consultation because of a whitish retrolental stain (leukocoria).

The bilateral form is rare (8).

Concerning the size of the affected area, the PERHS can be present in several ways. The consulted literature reports a great variability of presentations. The lack of regression can be:

A – Partial and be restricted: 1) to the posterior pole, compromising only the papilla (Bergmeister's papilla); 2) to the anterior pole, involving the lens and the tunica vasculosa lentis; and 3) only fluctuating remains in the vitreous, known as flying flies (Muscæ volitantes); and 4) Mittendorf's sign, a small whitish stain in the medial and posterior part of the lens.

B – Complete, starting from the papillary region, traversing all the eyeball up to the lens. In this case there is retraction of the embryonic retina, which becomes coiled forming a whitish mass behind the lens, which may lead to the suspicion of retinoblastoma.

The four cases presented here are of complete persistence.

COMPLEMENTARY TESTS

In addition to the routine tests like PET scans, ultrasound and so on, we highlight the Doppler, which shows the blood flow within the hyaloid artery in the cases of CPERHS (13). The use of Doppler was discussed elsewhere by Jacob, B.M. et al. (12).

LESIONS THAT MAY BE ASSOCIATED

Marshman and Jan (18) found associated neurological lesions, and in 7 unilateral cases 3 children were affected: hemiparesis, impaired coordination and homonymous hemianopsia; in 9 cases of bilateralism, 7 were ataxia, impaired coordination, hypotonia, spastic quadriplegia, microcephaly and deafness. They recommend neurological consultation in the cases of PHPV, especially in the bilateral forms. Other reported lesions were: microphthalmy, phthisis bulbae, glaucoma, congenital or acquired cataract, retinopathy of prematurity (12), and hypoplasia of the macula (3).In our series we found: retinal folds and retinal dysplasia.

◀ **FIGURE 7 –** a) Open eyeball. Section made in anteroposterior direction. See the retina forming pockets containing coagulated vitreous; its walls are side by side at the center. The cornea is normally convex. Right behind it, the Iris diaphragm allows to see the lens attached to its annular orifice. The lens, with decreased volume, is opaque, presenting fissures, and with an accentuated degenerative aspect. The retina is supported on the posterior portion of a granulomatous nodule formed of cholesterol crystals, examined in c. Then it extends, with duplicate appearance, until the posterior face of the lens, where it expands. There is no presence of a fibrous stalk such as in CPERHS. b) Leukocoria formed by retinal pockets and by the lens with cataract. c) Microscopic aspect of granuloma with cholesterol crystals, foamy cells containing lipids, and discreet gigantocytic reaction. HE. Magnification 20x. d) In the space between the walls of the retina there is subretinal exudation with voids left by the dissolved lipids. The vascular anomalies are noteworthy. HE. Magnification 4x. e-f) Throughout the extension of the wall the retina is embryonic, with folds or crypts and partial differentiations, never presenting as adult retina. In the transversal sections of the crypts there may appear aspects resembling rosettes, such as those in Figure E.

Observation: Figures C and D are pathognomonic for Coats'disease.

Retinoblastoma

a-b-c) Three aspects of leukocoria. In a, small whitish spot in eccentric location. In b, stain with reddish hue. In c, white, brilliant stain, corresponding to the classic amaurotic cat's eye brilliancy. d-e-f) Three macroscopic aspects. In d, the tumor forms peripheral clusters and several seeding spots in the vitreous. It may explain the small leukocoric stain. In e – Tumoral mass filling the eyeball, of variegated color, the red prevailing. Aspect compatible with retinoblastoma presenting extensive haemorrhagic areas, which may explain the reddish hue of the leukocoria. In f – White tumoral mass occupying the entire ocular chamber. There is invasion of the sclera and optic nerve.

Note: There is correspondence between the clinical manifestations and the pieces. Photo c, showing the typical glow of the amaurotic cat's eye, was gently contributed by Doctor Flávio Ferreira, to whom we pay our posthumous homage here. g-h-i-j) Several aspects of histological structure of retinoblastomas. In g, fleuretes of T´so, Fine, Zimmerman: Cells with long cytoplasmic photoreceptor processes that ressemble a bouquet of flowers. In h, Homer-Wright rosette: The cells are positioned around more or less homogeneous, finely fibrillary material. In i, Flexner-Wintersteiner rosette: The center of rosette is empty and limited by a thicker brim, like a membrane. In j, false rosette. The palisade cells are aligned around a vessel.

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ASSOCIATION WITH SYSTEMIC DISORDERS

Rare. It may be part of the *Incontinentia pigmentii* syndrome (5); be associated with septo-optic-pituitary dysplasia (de Morsier's syndrome), schizencephaly (3); with Knobloch syndrome – recessive autonomic disease, consisting in severe myopia, vitreoretinal degeneration with retinal detachment, malformation of the macula and occipital encephalocele, mapped in genetic studies as 21q22.3 (15), (7) – with trisomy 13, Norrie's disease, Warburg syndrome, cerebroocular-dysplasia-muscular dystrophy (3), retinopathy of prematurity (12).

DIFERENTIAL DIAGNOSIS

Leukocoria in childhood may be common in many diseases such as retinoblastoma, Coats' disease, retinopathy of prematurity, Norrie's disease, neonatal retinal detachment, and toxocariasis (12).

In our series we highlight retinoblastoma because of the pressing need for an early diagnosis, avoiding invasions of the optic nerve and other parts of the orbit, and Coats' disease because the funnel-shaped retinal detachment, with the apex inserted in the region of the papilla, may be confused with the complete persistence of the embryonic system.

GENETICS

It is a congenital lesion, most of the times without apparent cause. Rare cases proven to be gene-related were reported, such as affected twins (17) – the case described by Galal et al (8) is important because it suggests autosomal dominant inheritance, since many family members were affected: the father, the grandfather, two aunts, a paternal uncle and a grand-uncle with two daughters also affected. There is a report in which the authors claim to be the first to document autosomal dominant inheritance, as they wrote on June 02, 1990: "Although there are two previous reports of PHPV in siblings suggesting autosomal recessive inheritance, this is the first report compatible with autosomal dominant inheritance" (4). Another report in twins suggests autosomal recessive inheritance (17).

PATHOGENY

It is basically a failure in the regression mechanisms of the retinal and hyaloid systems. Many genes are involved in the process, both of development and regression, and the structures do their act *as puppets controlled by the hands of the genoma.* Numerous investigations have been carried out in this field (10) (11). We highlight as a curious fact the connection with regression mechanisms of tumor-suppressing genes.

The principle that any development is dependent not only on the complex of operating genes but also on the environment applies equally to the eye. The action of the internal environment is important but poorly known.

THERAPEUTICS

The persistence of the anterior primary vitreous – according to Appel et al, (Intraocular Tumors. Ed. Appleton/Century/Crofts. New York: 1975, p. 247), and also according to Sallum, J. and Hagemann, L. F. In: Doenças prevalentes da retina e vítreo – Lavinsky (SBRV). Ed. Cultura Médica, Rio de Janeiro: 2002, p. 417) – has attained good surgical results with lensectomy, membranectomy, and optical correction to prevent amblyopia.

PROGNOSIS

Compatible with long survival, most patients lose vision in the affected eye. The anterior form may attain vision of 20/70 or more if treated early with surgery (14).

SUMMARY AND CONCLUSION

With the presentation of four cases of CPERHS, the authors, based on data of Pathological Anatomy, propose abandoning the designation Persistent Hyperplastic Primary Vitreous proposed by Reese in 1955. With an evolutionary approach, they discuss the normal mechanisms of the formation and regression of the hyaloid system, the pathogeny of the persistence of this system, its manifestation and the procedures in the clinical approach, treatment and prognosis. In complete persistence, there is loss of vision in the affected eye. In the partial anterior persistence, it is possible to maintain a 20/70 vision or more with treatment.

The work shows the proper way of receiving and processing the eyeball in the laboratory in cases of leukocoria followed by enucleation, since randomly performed cuts may determine non-display of the persistent hyaloid system. The histopathological picture is important in the differential diagnosis with Coats' disease and retinoblastoma. They also conclude that it is wrong to say that there was retinal detachment, since it is the embryonic retina that did not evolve, did not differentiate itself, and formed the retrolental mass responsible for leukocoria. This is one of the reasons why the authors propose the label Complete Persistence of the Embryonic Retinal and Hyaloid Systems.

Finally, they conclude that in leukocorias one must always take into account the possibility of CPERHS.

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